J. Perinat. Med.
11 (1983) 67

Intra-ventricular hemorrhage and method of delivery of very low birth weight infants

G. Greisen, M. Block Petersen

Department of Neonatology and Laboratory of Child Pathology, Rigshospitalet, Copenhagen

1 Introduction

The possibilities of preventing intra-ventricular/sub-ependymal hemorrhage (IVH) are of greatest interest. Unfortunately only fragments are known of the pathogenesis [17, 18]. It has been pointed out that IVH is associated with gestational age, respiratory distress and vigorous resuscitation procedures. Only the latter is of any practical relevance to the clinician and calls for gentleness in handling and treatment of the very low birth weight infant (VLBW). Applying this gentleness in the obstetric management by way of delivering the very premature infant by cesarian section could conceivably contribute to the prevention of IVH.

2 Methods

The analysis includes all 152 VLBW infants admitted before 96 hours of age to the department of neonatology, Rigshospitalet, Copenhagen from October 1980 through March 1982.

The diagnosis of IVH was made by autopsy in all infants who died and by ultrasound examination (US) in the survivors. The US was done through the anterior fontanelle by the authors using a 5 MHz Aloka mechanical sector scanner as described by LEVENE [13].

Ten infants were not examined as they were discharged within few days to a local hospital and they are therefore excluded from the analysis of association of method of delivery to IVH. In cases where IVH was diagnosed, US was repeated approximately weekly until discharge from the department.

The surviving infants were classified according to the results of the series of US done as follow: 0) no IVH, 1) doubtful IVH not followed by ventricular dilatation, 2) IVH not followed by dilatation, 3) IVH followed by transient dilatation as judged from an increase in dimensions as well as a change in shape from slit-like to rounded, 4) IVH followed by dilatation which did not disappear, 5) IVH followed by dilatation and treated by ventriculo-peritoneal shunt. We found this classification more suited for the US than the conventional classification in grades 0-IV of PAPILE [15] developed for CT-scanning.

Curriculum vitae

GORM GREISEN *was born in 1951. He graduated from the university of Copenhagen in computer science 1974. Then he graduated from medical school Copenhagen 1976. His interests: Low birth weight, intra-venticular hemorrhage, cerebral blood flow and international child health.*

0300-5577/83/0011-0067$02.00

The clinical records from the first 96 hours of life were screened and the following data recorded: Birthweight; gestational age calculated from the last menstrual period checked by a clinical assessment of gestational age [6]; neonatal asphyxia was considered present in case of APGAR score ≤ 3 at 1 min. or ≤ 7 at 5 min. or umbilical artery pH < 7.00 or need for primary ventilation for more than 10 minutes after birth; arterial pH of less than 7.10, excluding the period immediately preceding death; arterial P_{CO_2} of more than 8.5 kPa; change of weight of more than 5% of birthweight in 24 hours; use of intubation and intermittent positive pressure ventilation.

For infants born per vaginam and by cesarian section the birthweights and gestational ages were compared by the t-test. Association between method of delivery and all other variables was examined by two way classifications and tested by calculating the Chi-square corrected for continuity. To examine the degree of reduction of risk of IVH in infants delivered by cesarian section the odds ratio (OR) was calculated as odds for IVH after cesarian section divided by the odds for IVH after vaginal delivery

$$\frac{(\{+\text{IVH/CS}\}/\{-\text{IVH/CS}\})/}{(\{+\text{IVH/vag}\}/\{-\text{IVH/vag}\})}$$

Finally a stepwise, multiple regression analysis was performed taking the presence of IVH grade 2–5 as the dependant variable and all other variables as explaining variables.

3 Results

152 infants were included. Mean birthweight was 1160 g (range 490–1500) and mean gestational age was 29.8 completed weeks (range 23–36). Twenty-nine infants (19%) died during admission at a mean postnatal age of 68 hours (0–288) hours.

One hundred and seventeen infants were delivered in the two obstetric departments at Rigshospitalet while 35 infants were transferred from other hospitals. 98 infants were delivered by cesarian section; in 36 cases no clinical contractions were recorded during the 24 hours preceding delivery. Of the 54 infants delivered per vaginam 7 were in breech presentation (3 had IVH).

The findings of IVH are tabulated in Tab. I, according to grade and method of delivery. In the survivors the diagnosis of IVH was certain in 42 infants (34%) while it was excluded in 61 infants (50%). The remaining 20 infants (16%) were either not examined by ultrasound or the results were equivocal.

Seven of the 9 infants without major IVH delivered per vaginam were immature (GA less than 27 weeks) and died within 12 hours of life. Six of the infants delivered by cesarian who died after 48 hours of life had major IVH in the form of ventricular casts, which most likely contributed to the death. Three other infants delivered by cesarian section were small for date, died and proved to have trisomia of the chromosome no. 18. Other recorded variables are summarized

Tab. I. IVH according to grade, survival and method of delivery.

	Survivors							Dead		
Grade of IVH	0	1	2	3	4	5	?	0	minor	major*
Per vaginam	15	5	10	5	4	1	3	4	5	2
Cesarian section	46	5	8	10	4	0	7	12	0	6
Total	61	10	18	15	8	1	10	16	5	8

* Bilateral IVH filling the entire lateral ventricles was classified as major.

Tab. II. Recorded variables according to method of delivery.

	Vaginal (n = 54)	Cesarian (n = 98)	P
BW	1120 g ± 247 g	1181 g ± 219 g	P < 0.001
GA	28.5 ± 2.4 weeks	30,5 ± 2.5 weeks	P < 0.001
Neonatal asphyxia	22/43	31/96	NS
pH < 7.10	7/45	15/92	NS
PCO_2 > 8.5 kPa	12/45	23/92	NS
Change of weight	20/38	33/82	NS
Ventilation	30/54	56/95	NS
IVH	27/51	28/91	P < 0.005
Death during admission	11/54	18/98	NS

according to method of delivery in Tab. II. In the group of infants delivered per vaginam IVH was more frequent ($P < 0.05$, OR = 0.58) but also mean birthweight was lower, mean gestational age was lower and there were more immature infants than in the group of infants delivered by cesarian section. There was no difference in risk of death during admission, in use of intubation and ventilation nor in the indicators of neonatal homeostasis.

As the two groups of infants differed in gestational age, which is known significantly to influence the risk of IVH, the material was stratified according to gestational age, which is shown in Tab. III. After correction for gestational age IVH remained less frequent in the infants delivered by cesarian section but this did no longer reach statistical significance.

$(x^2 = 0.65; P > 0.25)$.

In order to examine further the association between method of delivery and IVH stepwise, descending, multiple regression was carried out. The presence of IVH was taken as the dependant variable. Only 27% of the total variance could be explained by the complete set of explaining variables. Throughout the procedure GA remained the most significant explaining variable followed by ventilation. Cesarian section on its own could not clearly be demonstrated to be associated with a reduced incidence of IVH ($0.1 > P > 0.05$, one-tailed t-test). Exclusion of the 16 immature infants from the regression analysis did not change this finding.

Thus, some of the reduced incidence of IVH observed in the group of infants delivered by cesarian section was due to a slightly higher gestational age. Furthermore most of the variation in outcome as regards IVH remains unexplained.

Tab. III. Rate of IVH according to gestational age and method of delivery.

GA	Rate of IVH	Vaginal	Cesarian	Odds ratio
23–27	0.44	6/12	1/4	0.33
27–28	0.68	12/18	14/18	1.75
29–30	0.46	8/13	8/22	0.36
31–32	0.24	1/7	5/26	1.42
33–36	0.0	0/1	0/19	–
Total	0.39	27/51	28/91	–
expected*	–	24.9	30.1	0.85**

* calculated as the sum of the expected number of IVH in each GA-group on basis of the GA-specific rate of IVH.

** calculated as the weighted mean after linarization using log (OR)

4 Discussion

The purpose of the present study was to examine whether use of cesarian section for delivery of the VLBW infant, irrespective of fetal presentation, can be expected to reduce the risk of IVH. This would be of immediate clinical relevance in a situation where the pathogenesis is only incompletely known.

US was introduced in our department early 1980 and was soon done routinely by the authors on all VLBW infants. Thus a consecutive series of infants with IVH diagnosed by a single criterion (excluding autopsy) was available for a cohort study.

US by sector scanner through the anterior fontanelle has been accepted as a reliable method for detecting IVH [16] although results have been reported to be equivocal in a small number of infants [14].

Classification of increases in density in the region of the head of the caudate appears to be the most important weakness of the US. They can be considered as minor subependymal hemorrhages which may be seen only on a single occasion or they can be considered as artefacts of unknown origin. Even if these increases in density do represent small hemorrhages they may not have any negative bearings on the prognosis of the infant, so from the clinical point of view this uncertainty may not be important. But any noticeable degree of uncertainty (in the present analysis 10 such cases were recorded, but others may still have been misclassified) will considerably reduce the observed statistical association between IVH and any relevant predisposing factor. We have chosen to consider the infants with equivocal US as being without significant IVH for the purpose of statistical analysis. Our gross rate of IVH of 39% is in good agreement with most reports.

Our analysis clearly demonstrates that VLBW infants delivered by cesarian section are at reduced risk of IVH when compared to those delivered per vaginam. Several authors have reported on the association between cesarian section and IVH [1, 2, 3, 4, 5, 8, 9, 12, 14]. Wherever the published data have permitted, the odds ratio (OR) and CHI-square of the 2 x 2 contigency tables have been computed and the results are shown in Tab. IV. In all but one case the OR is well below unity although in no instance the risk of IVH in infants delivered by cesarian section is sufficiently reduced to produce statistical significance in view of the limited number of infants in each individual study (type II error).

Unfortunately the comparability of the infants delivered by cesarian section and those delivered per vaginam is uncertain, as well as the comparability of the preceding pregnancy.

The data available to the attending obstetrician and the set of indications used for deciding the method of delivery are very important. It is not possible to analyse this in detail in a retrospective study covering several obstetric departments. But at least breech presentation and twin pregnancy were routinely managed by cesarian section.

Furthermore the recorded data may not be completely descriptive for instance, neither the APGAR score nor the umbilical artery pH may fully reflect the axphyxiating process.

We have tried to correct for the influence of confounding variables by calculating the GA-specific incidences of IVH in the two groups as well as by use of the more general approach of multiple regression analysis. The result of both procedures is a reduction of the difference to a subsignificant level but with a persisting trend.

Tab. IV. Summarized data on IVH and method of delivery from 7 reported series of VLBW infants.

Author	Population characteristic	Method of diagnosis	No.	Rate of IVH	Rate of CS	OR	P-value
GARCIA-PRATS et al.**	⩽ 1500 g and 32 w	clinical + CT	220	0.44	0.19	0.61	< 0.1
DYRKES et al.	⩽ 35 w	CT	151	0.42	0.30	0.65	NS
HAESSLIN and GOODLIN	⩽ 1350 g	clinical	100	0.19	0.30	0.38	NS
KOSMETOS et al.	⩽ 1500 g	CT	64	0.58	0.28	0.34	NS
CLARK et al.	⩽ 1250 g	CT	60	0.32	0.27	1.43	NS
COOKE	⩽ 1500 g	US	39	0.51	0.28	0.72	NS
BEJAR et al.	⩽ 1000 g and ⩽ 33 w	US	28	0.82	0.43	0.43	NS
Present analysis	⩽ 1500 g	US	142	0.39	0.66	0.58	< 0.05

** recalculated from published percentages.

KOSMETATOS reports a statistical significant effect of mode of delivery through a multiple regression analysis [12].

The timing of IVH within the first day of life in the majority of cases [4] points at causal factors operating during labor, delivery and the first few hours of life. A pathogenetical model involving changes in cardio-respiratory function, changes in blood pressure and cerebral blood flow as well as a result of an impaired autoregulation has been commonly proposed [17, 18]. A close time-relationship of IVH to pneumothorax with profound changes in systemic hemodynamics has recently been reported [10]. It is straightforward to associate the much more common occurrence of IVH in the first day of life to the stress of delivery. Cesarian section aiming at minimizing physical and anoxic trauma could well be expected to reduce the risk of these early hemorrhages. On the other hand cesarian section carries an increased risk of respiratory distress [11] which is a predisposing factor for IVH, eventually later than the first day of life. Unfortunately our US were not sufficiently frequent to allow a timing of the IVH.

A controlled, ramdomized, clinical study testing the effect of mode of delivery would be very useful. But such a study would be difficult to carry through, as a minimum of 80 infants would be required in each group to detect a reduction of risk by 50%. To carry out a randomization procedure in the swiftly changing clinical setting of imminent premature labor or delivery would be very demanding if not impossible.

We therefore believe that clinicians will have to do with indirect evidence as that presented and reviewed here and we find that it points at liberal use of cesarian section for the delivery of the VLBW infant regardless of fetal presentation.

Summary

One hundred and fifty-two infants with birthweight $\leq$ 1500 g admitted consecutively to a tertiary NICU are reported. Autopsy was done in all 29 infants who died, IVH was present in 13. Ultrasound scanning through the anterior fontanelle was done in 113 survivors; IVH was found in 42. Ninety-eight infants were delivered by cesarian section and IVH was less frequent in these infants: 28/91 compared to 27/51 in the infants delivered per vaginam. (Odds ratio = 0.58, $P < 0.05$). Gestational age was higher (30.5 ± 2.5 weeks) in the infants delivered by cesarian section than in the infants delivered per vaginam (28.5 ± 2.4 weeks). After correction for difference in gestational age the trend consistently showed reduced incidence of IVH after cesarian section (odds ratio = 0.85) but the difference did no longer achieve statistical significance. Information on neonatal asphyxia, intermittent positive pressure ventilation, acidosis, hypercarbia and rapid change of weight during the first 96 hours of life was collected from clinical records. **A multiple regression analysis showed increased risk of IVH with low gestational age and with use of intermittent positive pressure ventilation.** The effect of cesarian section was only sub-significant ($0.1 > p > 0.05$: one-tailed t-test). The results of 7 previous reports on the association between method of delivery and IVH are reviewed (Tab. IV); in all but one the risk of IVH was reduced after cesarian section although in no case the difference did reach statistical significance.

The problem of achieving comparability between groups of infants delivered by cesarian section and per vaginam are discussed as a controlled randomized study can be considered as impractical. The recent reports of very early occurrence of IVH in a majority of cases points at stress during delivery to be an important causal factor. This is further suggested by the proposed pathogenesis of IVH involving changes of blood-gases, blood pressure and of loss of autoregulation of cerebral blood flow. We conclude that the available evidence indicate liberal use of cesarian section for the delivery of the very low birth weight infant regardless of foetal presentation.

Keywords: Cesarian section, intra-ventricular hemorrhage, very low birth weight.

Zusammenfassung

Intraventrikuläre Blutungen und Entbindungsmodus bei stark untergewichtigen Neugeborenen

Wir berichten über 152 Neugeborene mit einem Geburtsgewicht $\leq$ 1500 g, die auf einer Intensivstation überwacht wurden. Bei allen 29 Kindern, die gestorben sind, wurde eine Obduktion durchgeführt. Das Ergebnis war eine intraventrikuläre Blutung in 13 Fällen. Eine Ultraschalluntersuchung über die große Fontanelle führten wir bei 113 überlebenden Kindern durch, wobei in 42 Fällen eine intraventrikuläre Blutung nachweisbar war. 98 Kinder wurden per Sectio geboren; im Vergleich zu vaginalen Entbindungen traten intraventrikuläre Blutungen nicht so häufig auf (28/91 bzw. 27/51; odds ratio = 0.58, $p < 0.05$). Das Schwangerschaftsalter betrug bei den per

Sectio geborenen Kindern 30.5 ± 2.5 Wochen, bei den vaginal geborenen Kindern 28.5 ± 2.4 Wochen. Auch nach der Korrektur bezogen auf das Schwangerschaftsalter zeigte sich die Tendenz, daß intraventrikuläre Blutungen nach Sectiones weniger häufig auftraten, jedoch war der Unterschied nicht mehr statistisch signifikant (odds ratio = 0,85). Klinische Daten wie das Auftreten einer neonatalen Asphyxie, die Notwendigkeit einer intermittierenden Beatmung mit positiven Drucken, das Vorliegen einer Azidose und Hyperkapnie sowie rasche Gewichtsänderung in den ersten 96 Lebensstunden wurden berücksichtigt. **Eine multiple Regressionsanalyse zeigte ein hohes Risiko einer intraventrikulären Blutung bei kurzer Schwangerschaftsdauer und intermittierender Beatmung mit positiven Drucken**; der Einfluß durch den Entbindungsmodus trat zurück ($0.1 > p > 0.05$ bei Anwendung des t-Tests). Tab. IV zeigt die Ergebnisse von 7 Arbeiten, die den Zusammenhang von Entbindungsmodus und intraventrikulärer Blutung untersuchten. Bis auf eine Ausnahme haben diese Arbeiten ergeben, daß intraventrikuläre Blutungen nach Sectio weniger häufig auftraten, obwohl keine statistisch signifikanten Unterschiede gesichert werden konnten.

Das Problem ist, eine Vergleichbarkeit zwischen der Gruppe von vaginal und per Sectio geborenen Kindern herzustellen. Kontrollierte randomisierte Studien sind praktisch nicht durchführbar. Neuere Arbeiten, die über ein sehr frühes Auftreten von intraventrikulären Blutungen berichten, weisen in der Mehrzahl der Fälle den Geburtsstress als einen wichtigen ursächlichen Faktor aus. Dies wird unterstützt durch die pathogenetischen Vorstellungen bezüglich der Entstehung einer intraventrikulären Blutung, die Änderungen der Blutgaswerte und des Blutdrucks sowie einen Autoregulationsverlust der Hirndurchblutung beinhalten. Wir meinen, daß bei Kindern mit extrem niedrigem Geburtsgewicht unabhängig vom fetalen Status eine Sectio offensichtlich indiziert ist.

Schlüsselwörter: Extrem niedriges Geburtsgewicht, intraventrikuläre Blutung, Sectio caesarea.

Résumé

Hémorragie intra-ventriculaire et mode d'accouchement des enfants de très bas poids de naissance

Les auteurs ont étudié 152 enfants de poids de naissance ⩽ 1500 g.

Une autopsie a été réalisée sur les 29 enfants décédés; une HIV existait chez 13. Une échographie trans-fontanellaire antérieure a été pratiquée chez les 113 survivants; une HIV a été trouvée chez 42. 98 enfants sont nés par césarienne et l'HIV est moins fréquente chez ces enfants: 28/91 contre 27/51 chez les enfants nés par voie basse. (rapport = 0.58, $p < 0.05$). L'âge gestationnel est plus élevé (30.5 ± 2.5 semaines) chez les enfants nés par césarienne que celui des enfants nés par voie basse (28.5 ± 2.4 semaines). Après correction de la différence d'âge gestationnel, il apparaît une tendance ferme d'une diminution de l'incidence de l'HIV après césarienne (rapport = 0.85) mais la différence n'est pas statistiquement significative. Parmi les données cliniques, ont été collectées les informations sur une asphyxie néonatale, une ventilation à pression positive intermittente, une acidose, une hypercapnie, et une variation de poids rapide au cours des 96 premières heures de vie. **Une analyse à variables multiples montre un risque accru d'HIV pour les bas âges gestationnels et lors de l'utilisation d'une ventilation à pression positive intermittente.** L'effet de la césarienne n'est que faiblement significatif ($0.1 < p < 0.05$).

Les résultats des 7 études antérieures sur l'association entre le mode d'accouchement et l'HIV sont passés en revue (Tab. IV); dans toutes sauf une, le risque d'HIV est diminué après césarienne bien que pour aucune la différence ne soit statistiquement significative.

Les auteurs discutent le problème de l'équivallence des groupes d'enfants nés par césarienne et par voie basse de même que la réalisation d'une étude randomisée qui peut être considérée comme impossible à réaliser. Les données récentes sur la survenue très précoce d'HIV dans la majorité des cas mettent l'accent sur le stress pendant l'accouchement comme important facteur causal. Cela est en outre suggéré par la pathogénie proposée de l'HIV englobant les modifications des gaz du sang, de la pression sanguine et de la perte de l'autorégulation de la circulation sanguine cérébrale. Les auteurs concluent que les données disponibles sont en faveur d'une utilisation libérale de la césarienne pour la naissance des enfants de très bas poids de naissance quelle que soit la présentation.

Mots-clés: Césarienne, hémorragie intra-ventriculaire, poids de naissance très faible.

Bibliography

[1] BEJAR, R., V. CURBELO, R. W. COEN, G. LEOPOLD, H. JAMES, B. SAUNDERS, R. PORECO, L. GLUCK: Incidence of intraventricular and germinal layer hemorrhage (IVH/GLH) in preterm infants born pervagina and c-section. Pediat. Res. 14 (1980) 629

[2] CLARK, C. E., R. I. CLYMAN, R. S. ROTH, S. H. SNIDERMAN, B. LANE, R. A. BALLARD: Risk factor analysis of intraventricular hemorrhage in low-birth-weight infants. J. Pediat. 99 (1981) 625

[3] COOKE, R. W. I.: Factors associated with periventricular hemorrhage in very low birthweight infants. Arch. Dis. Child. 56 (1981) 425

[4] CRESPIGNY, L. CH. DE, R. MACKAY, L. J. MURTON, R. N. D. ROY, P. H. ROBINSON: Timing of neonatal cerebroventricular hemorrhage with ultrasound. Arch. Dis. Child. 57 (1982) 231

[5] DYKES, F. D., A. LAZZARA, P. AHMANN, B. BLUMENSTEIN, J. SCHWARTZ, A. W. BRANN: Intraventricular hemorrhage: A prospective evaluation of etiopathogenesis. Pediatrics 66 (1980) 42

[6] FINNSTRÖM, O.: Studies on maturity in newborn infants. Acta Paediat. Scand. 61 (1972) 24
[7] FRIIS-HANSEN, B., H. C. LOU, N. A. LASSEN, P. D. WIMBERLEY: The pathogenesis of cerebral hypoxic lesions and intraventricular hemorrhage in the newborn preterm infant. In: STERN, L., B. SALLE, B. FRIIS-HANSEN (eds.): Intensive care of the newborn III. Masson, USA 1981
[8] GARCIA-PRATS, J. A., R. S. PROCIANOY, J. ADAMS, A. J. RUDOLPH: The hyaline membrane disease – intraventricular hemorrhage relationship in the very low birth weight infant: Perinatal aspects. Acta Paediat. Scand. 71 (1982) 79
[9] HAESSLEIN, H. C., R. C. GOODLIN: Delivery of the tiny newborn. Amer. J. Obstet. Gynec. 134 (1979) 192
[10] HILL, A., J. M. PERLMAN, J. J. VOLPE: Relationship of pneumothorax to occurrence of intraventricular hemorrhage in the premature newborn. Pediatrics 69 (1982) 144
[11] HJALMARSON, O., KRANTZ, B. JACOBSSON, S. E. SÖRENSEN: The importance of neonatal asphyxia and caesarean section as risk factors for neonatal respiratory disorders in an unselected population. Acta Paediat. Scand. 71 (1982) 403
[12] KOSMETATOS, N., C. DINTER, M. L. WILLIAMS, H. LOURIE, A. S. BERNE: Intracranial hemorrhage in the premature. Amer. J. Dis. Child. 134 (1980) 855
[13] LEVENE, M. I., J. S. WIGGLESWORTH, V. DUBOWITZ: Cerebral structure and intraventricular hemorrhage in the neonate: A real-time ultrasound study. Arch. Dis. Child. 56 (1981) 416
[14] LEVENE, M. I., FAWER, R. F. LAMONT: Risk factors in the development of intraventricular hemorrhage in the preterm neonate. Arch. Dis. Child. 57 (1982) 410
[15] PAPILE, L. A., J. BURSTEIN, R. BURSTEIN, H. KOFFLER: Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1.500 grams. J. Pediat. 92 (1978) 529
[16] VOLPE, J. J.: Anterior fontanel: Window to the neonatal brain. J. Pediat. 100 (1982) 395
[17] WIGGLESWORTH, J. S., K. E. PAPE: Pathophysiology of intracranial hemorrhage in the newborn. J. Perinat. Med. 8 (1980) 119
[18] WIMBERLEY, P. D., H. C. LOU, M. HEJL, N. A. LASSEN, B. FRIIS-HANSEN: Hypertensive peaks in the pathogenesis of intraventricular hemorrhage in the newborn. Abolition by phenobarbitone sedation. Acta Pediat. 71 (1982) 537

Received October 12, 1982. Accepted December 14, 1982.

Gorm Greisen
Dept. of Neonatology
Rigshospitalet
University Hospital
9 Blegdamsvej
DK-2100 Copenhagen Ø
Denmark